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Leherte, Laurence; Vercauteren, Daniel

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Determination of protein coarse grain charges from smoothed molecular electrostatic potentials

Laurence Leherter, Daniel P. Vercauteren

Laboratoire de Physico-Chimie Informatique, Groupe de Chimie Physique Théorique et Structurale, University of Namur (FUNDP)

Introduction

The design of coarse grain (CG) models [1] and their corresponding potential functions [2] for protein computational studies is currently an active field of research, especially in solving long-scale dynamics problems such as protein folding, protein-protein docking, ... For example, to eliminate fast degrees of freedom, it has been shown that one can rely on CG representations only, or on mixtures of CG and more detailed descriptions [3,4] in order to significantly increase the time step in molecular dynamics (MD) simulations. Among the parameters involved in CG potentials, the electrostatic interactions are of major importance [5] since they govern local and global properties such as their stability [6], their flexibility [7], ...

In this poster, we present an approach to design and evaluate CG electrostatic point charges from smoothed molecular electrostatic potentials (MEP). In a previous approach [8], electron density (ED)-based CG were determined through a merging/clustering procedure of atom trajectories generated in progressively smoothed ED distribution functions. In the present work, atoms are clustered according to their trajectories defined in a smoothed MEP function, more particularly the Amber potential reported in [9]. A fitting algorithm is applied to evaluate CG charges.

1. Location of CG points

A hierarchical merging algorithm, based on the idea of Leung *et al.* [10], is used to locate local maxima and minima in a MEP function V , as a function of the degree of smoothing t .

1. At scale $t = 0$, each atom of a molecular structure is considered as a local maximum or minimum of V . All atoms are thus considered as the starting points of the merging procedure.

2. As t increases from ~ 0.0 to a given maximal value, each point moves continuously along a gradient path to reach a location in the 3D space where:

$$\vec{\nabla} V(t) = 0$$

On a practical point of view, this consists in following the trajectory of the points within the MEP function calculated at t according to Equation:

$$\vec{r}_V(t) = \vec{r}_V(t-\Delta t) + \frac{\Delta}{V(t)} \vec{\nabla} V(t)$$

2. Molecular electrostatic potential

$$V_A(\vec{r}) = \sum_{a \in A} \frac{Z_a}{|\vec{r} - \vec{R}_a|}$$

$$V_{A,t}(\vec{r}) = \sum_{a \in A} \frac{Z_a}{|\vec{r} - \vec{R}_a|} \operatorname{erf} \left(\frac{|\vec{r} - \vec{R}_a|}{2\sqrt{t}} \right)$$

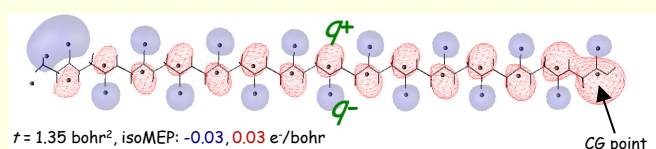
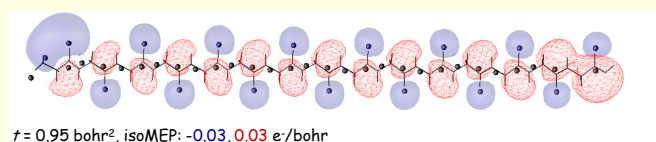
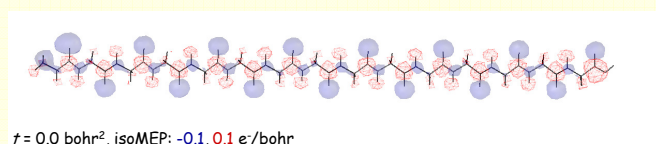
3. Determination of CG charges

This is achieved through the program QFIT [11] to get CG point charges fitted from an unsmoothed MEP grid, considering the following constraints: the total molecular charge and dipole.

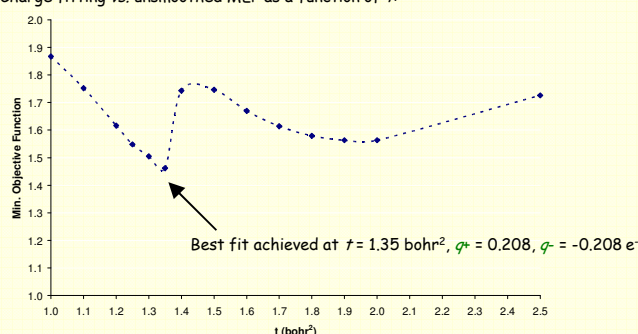
4. Determination of backbone CG charges

a) Construction of Gly₁₅ in an extended conformation ($\Omega = 180^\circ$, $\Phi = -139^\circ$, $\Psi = 135^\circ$) using SMMP05 [12], a Monte Carlo/Simulated Annealing program.

b) Application of the hierarchical merging/clustering algorithm



b) Charge fitting vs. unsmoothed MEP as a function of t



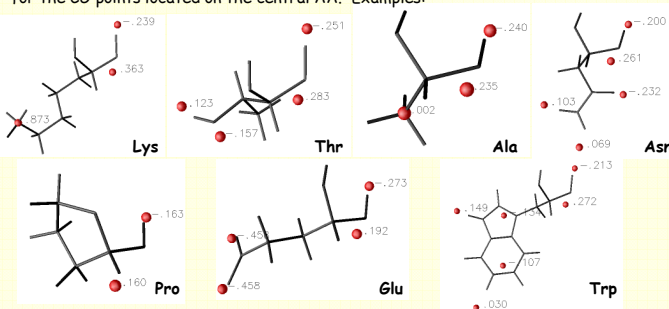
5. Determination of CG charges of amino acid (AA) side chains

a) Construction of Gly7-AA-Gly7 in an extended conformation ($\Omega = 180^\circ$, $\Phi = -139^\circ$, $\Psi = 135^\circ$) with various AA rotamers [13] using SMMP05 [12]. Examples:

	Conformation	$\chi^1 (^\circ)$	$\chi^2 (^\circ)$	$\chi^3 (^\circ)$	$\chi^4 (^\circ)$	Occurrence (%)
Arg	g-, t, g-, g-	300	180	300	300	9.5
	g-, t, g-, t	300	180	300	180	11.9
	g-, t, g+, t	300	180	60	180	12.2
	g-, t, t, t	300	180	180	180	12.2
Asn	t, Nt	180	0			11.1
	t, Og-	180	300			21.3
	t, Og+	180	60			23.6

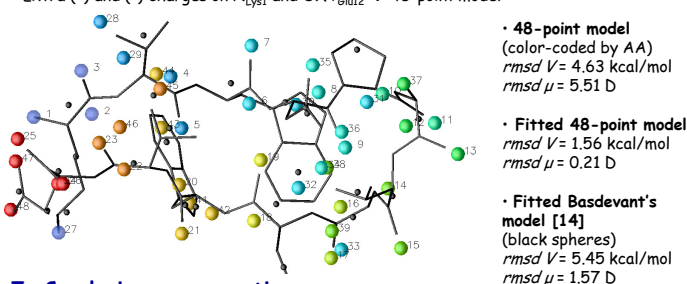
b) Use of CG points obtained at $t = 1.35 \text{ bohr}^2$ (see sections 1 and 2)

c) CG Charge fitting with additional constraints: Gly₁₅ charges (see section 3) except for the CG points located on the central AA. Examples:



6. Application to 12-residue β -hairpin HP7 [14]

- (2+)Lys-Thr-Trp-Asn-Pro-Ala-Thr-Gly-Lys(-)-Trp-Thr-Glu(2-)
- Positioning of CG points through QUATFIT, a superposition algorithm [15], using the above templates and the PDB structure of HP7 (2evq.pdb)
- Extra (+) and (-) charges on N_{Lys1} and OXT_{Glu2} \rightarrow 48-point model



7. Conclusions, perspectives

- A CG model built from a smoothed MEP
 - seems to be a more significant electrostatic model than a description based on AA centers-of-mass as reported in [14]
 - can be derived for any set of point charges (Amber, Gromos, ECEPP, ...)
- Transferability has to be confirmed

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